5. (Amended) The DNA sequence according to any of claims 2 to 4 in which said substituted or inserted amino acid is [taken from the list] selected from the group consisting of Asn, Asp, Arg, Gln, Glu, Gly, His, Lys, Ser, and Thr.

REMARKS

Claims 1-27 are pending in this application.

Applicants have amended the specification to include a definition of the term "association domain". Support for this amendment can be found in claims 23-25 as originally filed.

Applicants have amended claim 1 to more distinctly claim the subject matter of the invention. Specifically, applicants have amended claim 1 to recite that the IGSF encoded by the claimed DNA sequence would retain the ability to bind antigen. Support for this amendment can be found in the specification as originally filed, for example on page 22, line 30 - page 23, line 5. Claim 1 was also amended to recite "domain or fragment" after "said IGSF". This amendment is done for the purpose of clarity and is supported by the claim as originally filed. Finally, applicants amended claim 1 to recite that the two domains which comprise the interface are contiguously adjoined.

Support for this amendment can be found in the specification, for example on page 5, lines 1-4. No support

Applicants have amended claim 5 to more distinctly claim the subject matter of the invention. Specifically, applicants have amended claim 5 so that it recites the proper Markush format.

Objections

The Examiner has objected to the disclosure on page 23, line 18 because the word "algorithm" was incorrectly spelled. Applicants have amended the specification to obviate this objection.

The Examiner has also objected to the specification contending that there is not proper antecedent basis for the term "association domain." Applicants have amended the specification to incorporate a definition of the term, thus obviating the objection.

Claim Rejections - 35 U.S.C. § 112, first paragraph

Claims 1-9, 11, and 13-27 stand rejected under 35 U.S.C. § 112, first paragraph because the Examiner contends that these claims are not enabled by the specification. Specifically, the Examiner contends that the specification does not disclose "sequence data regarding a modification conferring increased hydrophilicity of any DNA sequence

comprising a sequence that encodes a modified Fab fragment, an Fv fragment, or an Fv fragment stabilized by an inter-domain disulphide bond...or a DNA sequence encoding any modified immunoglobulin superfamily domain or fragment". Applicants traverse.

The basis for the present invention is the surprising discovery that the solubility of antibody fragments comprising at least one domain can be dramatically increased by decreasing the hydrophobicity of regions corresponding to interfaces in a native antibody molecule at the end of the domain. In other words, an IgSF domain or fragment is modified at the interface end that would normally be found between contiguous domains. This discovery is surprising because the end of the domain is quite small in proportion to the surface area of the molecule and would be expected to play less of a role in determining the physical properties of the molecule. Applicants further disclose how to identify which residues should be modified (for example, page 6, line 16 - page 7, line 3), how to modify the residues (for example, page 7, lines 4-30), and which modifications are preferred (for example, page 7, line 31 - page 8, line 6).

In order to satisfy the enablement requirement of § 112, it is not necessary or desirable for applicants to supply sequence data for each and every embodiment

encompassed in the claims. Enablement does require, however, that the specification teach one of skill in the art how to practice the invention as claimed without undue experimentation. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There, the Court stated, "enablement is not precluded by the necessity for some experimentation such as routine screening. . . . experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not experimentation.'" *Id.* at 1404.

In the instant application, the Examiner has stated that the most relevant factors on which her rejection is based are the scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented. See, e.g., Ex parte Forman, 230 USPQ 546, 547 (Bd. Pat. Appl. & Inter. 1986). However, applicants have demonstrated that potential residues for modification can be "predicted" based on the guidance provided in the specification (See page 6, line 16 - page 7, line 3). Further, applicants have demonstrated that, once the predicted residues have been modified, it requires only routine experimentation to resolve which "predictions" result in proteins of increased solubility.

The Examiner additionally states that there is a lack of knowledge regarding which modifications would confer increased hydrophilicity and additionally result in a

modified molecule capable of functioning in the same way as the parent molecule. However, the existence of an inoperative embodiment within the scope of the claim does not necessarily render the claim nonenabled. The standard is whether a skilled person could determine which embodiments would be inoperative or operative with the expenditure of effort normally required in the art. Atlas Powder Co. b. E.I. du Pont de Nemours & Co., 750 F.2d 1569. Once again, the analysis of applicants' embodiments can be performed by one of skill in the art through routine experimentation (as described by applicants in Example 1).

It is clear that practitioners in the art would expect to practice routine experimentation to arrive at and optimize the sequences described in applicants' specification. The present situation is similar to the field of monoclonal antibodies considered by the Federal Circuit in *In re Wands*. In re Wands, 8 USPQ2d 1400, (Fed. Cir. 1988). There, the Court held that screening of a large number of negative hybridomas does not render the field unpredictable, because "practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Id* at 1406. Similarly, practitioners in the field of mutagenesis are prepared to sequence and mutagenize large numbers of DNA sequences when developing promising candidates for expression.

Furthermore, and contrary to the Examiner's contention, the present specification provides guidance and working examples for manipulating the variables necessary to achieve the DNA sequences of the instant invention. Example 1, for instance, describes the residue by residue analysis of 30 non-redundant Fab fragments and their corresponding Fv fragments. Applicants describe the routine analysis specifically, for example, with respect to the 4-4-20 scFv fragment (page 19, starting at line 5). Applicants describe creating three different modifications to the fragment and testing each one for expression (page 20, lines 5-17), and describe the 25 fold increase in soluble protein seen with one of the modified fragments. It is clear that a similar analysis could be conducted with any of the claimed domains or fragments. Therefore, this disclosure provides a road map for one of skill in the art to use in creating the DNA sequences of the instant invention.

Additionally, it would not be feasible for applicants to provide similar details on every DNA sequence which may be modified according to the present invention. This would require a specification of immense length. Considering the specification in light of the amount of knowledge in the art, one of skill in the art can practice applicants' invention. The Examiner has provided no scientific reason why applicants should be limited to the

DNA sequences exemplified in the examples of the instant specification.

In view of the amended claims and the arguments presented herein, applicants request that the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, second paragraph

Claims 1-27 stand rejected under 35 U.S.C. § 112, second paragraph because the Examiner contends they fail to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner contends that claims 23-25 are indefinite in the recitation of the term "association domain". Applicants traverse.

Applicants have amended the specification herein to define the term association domain. As described above, support for this amendment can be found in originally filed claims 23-25. Based on this disclosure and the clear meaning of the terms to one of skill in the art, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 23-25 under 35 U.S.C. § 112, second paragraph.

Claim 1 (and its dependent claims) stand rejected because the Examiner contends that the claim is unclear

based on the recitation "wherein said modified IGSF differs". Applicants have obviated this rejection by amending claim 1 to recite "wherein said modified IGSF fragment or domain differs", thus obviating this rejection.

Claim 5 stands rejected because the Examiner contends that it is not in proper Markush format. Applicants have obviated this rejection by amending the claim as suggested by the Examiner.

35 U.S.C. § 102(a)

Claims 1-2, 5-7, 10, 12-13, 18-22, and 26-27 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Neiba et al. (Protein Engineering 10(4): 435-444 (1997)). Applicants have obviated this rejection by submitting herewith a certified copy of the priority document in accordance with 37 C.F.R. 1.55.

35 U.S.C. § 102(b)

Claims 1-7, 10, 13-17, and 26-27 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Johnson et al. (WO 92/01787)("Johnson"). Specifically, the Examiner states that Johnson teaches "an analogue of a single chain variable domain of a member of an immunoglobulin or immunoglobulin superfamily, in which said analogue one or more interface amino acid residues of the domain are

altered" such that the anologue is more hydrophilic than the unaltered domain. Applicants traverse with respect to Johnson's applicability to the instant application.

As described in applicants' instant specification, Johnson teaches that "isolated single domains, e.g. VH, can be modified in the former VL/VH interface region..." (page 3, lines 18-19). Clearly then, Johnson's definition of "interface" is much different than applicants' use of the term "interface". The "VL/VH interface" described in Johnson is not between "contiguously adjoined" domains as recited in applicants' amended claim 1, but instead exists between distinct polypeptides. Johnson states:

> [t]he present applicant has realised that the most likely cause of the unfavourable properties of single domain antibodies is the exposure to aqueous solvent, of the hydrophobic face of a single variable domain eg. the VH single domain. In native antibodies, this face interacts with the adjacent hydrophobic face of the VL domain and is buried within the antibody molecule. Johnson, Page 3, lines 3-9.

Thus, it is apparent that the use of the term "interface" in Johnson is referring to a completely different interface than that which is referred to in the instant claims.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

35 U.S.C. § 103

Claims 1-7, 10, 13-17, 18-22, and 26-27 stand rejected under 35 U.S.C. § 103(a) because the Examiner contends that they are unpatentable over Johnson in view of Jenkins et al. (PNAS 92:6057-6061, 1995) ("Jenkins") and Knappik et al. (Biotechniques 17(4): 754-761, 1994) ("Knappik"). Specifically, the Examiner contends that Jenkins and Knappik provide the teaching that Johnson lacks with respect to claims 18-22. Applicants traverse.

However, as described above, Johnson does not teach or suggest applicants' instant invention. Further, the combination of Jenkins or Knappik, which the Examiner cites for teaching additional moieties, adds nothing to make up for the lack of teaching in Johnson regarding the DNA sequence itself. For this reason, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103.

Conclusion

For all of the above reasons, reconsideration and allowance of the pending claims is requested.

Respectfully submitted,

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